Influence of the Angiotensin II Antagonist Valsartan on Left Ventricular Hypertrophy in Patients With Essential Hypertension

Petra A. Thürmann, MD; Peter Kenedi, MD; Andor Schmidt, MD; Sebastian Harder, MD; Norbert Rietbrock, MD

Background—Left ventricular hypertrophy (LVH) represents an independent risk factor in patients with essential hypertension. Because reversal of LVH may be associated with an improvement of prognosis, the influence of new antihypertensive compounds, such as angiotensin II AT₁ receptor antagonists, on LVH should be determined.

Methods and Results—In a randomized, double-blind trial, 69 predominantly previously untreated hypertensive patients with echocardiographically proven LVH, ie, left ventricular mass index (LVMI) >134 g/m² in men and >110 g/m² in women and/or end-diastolic septal thickness >12 mm, received either the angiotensin II antagonist valsartan or atenolol for 8 months. Echocardiographic data of 58 patients were available. After 8 months of valsartan treatment (n=29), LVMI decreased from 127±23 to 106±25 g/m² (ratio [R]=0.83; 95% CI, 0.79 to 0.87; P<0.0001 versus baseline). Under atenolol (n=29), LVMI decreased to a smaller extent, from 127±25 to 117±27 g/m² (R=0.92; 95% CI, 0.86 to 0.98; P=0.0082 versus baseline). The mean reduction of LVMI came to 21 g/m² under valsartan and only to 10 g/m² under atenolol (R=0.91; 90% CI, 0.85 to 0.97 versus atenolol). Baseline mean blood pressure values were determined to be 163±12/101±6 mm Hg before treatment with valsartan and 160±14/103±6 mm Hg before atenolol treatment. After 8 months of treatment, mean blood pressure decreased to 146±13/90±7 mm Hg with valsartan and to 147±18/90±7 mm Hg with atenolol. Nine patients in the valsartan group and 8 patients in the atenolol group required additional medication with hydrochlorothiazide.

Conclusions—Antihypertensive treatment with the angiotensin II antagonist valsartan for 8 months produced a significant regression of LVH in predominantly previously untreated patients with essential hypertension. The drug may be safely administered in this subset of hypertensive patients; however, the long-term benefit in terms of risk reduction has still to be evaluated in further trials. (Circulation. 1998;98:2037-2042.)

Key Words: hypertension • hypertrophy • ventricles • angiotensin

...In hypertensive patients, left ventricular hypertrophy (LVH) represents a powerful predictor for cardiovascular morbidity and mortality independent of other cardiovascular risk factors, even blood pressure itself. Regression of LVH may be associated with an improvement of prognosis. Meta-analyses and a recently published trial comparing the effects of different drug classes on LVH have suggested that ACE inhibitors are currently the most powerful drugs in this regard. In contrast, recently published prospective trials comparing the effects of different drug classes revealed no relevant differences in terms of LVH reduction, and the question of whether antihypertensive drugs differ in their ability to regress LVH was put forward. Considering the importance of LVH as an independent risk factor, the safety and efficacy of new antihypertensive drugs in patients with LVH have to be studied.

In addition to a chronic increase in pressure and/or volume overload, an elevation in plasma ACE activity, plasma aldosterone levels, and angiotensin II (Ang II) concentrations play a major role in the development of LVH. Reduction of Ang II levels after ACE inhibition may be responsible for the beneficial effects of ACE inhibitors beyond the blood pressure–lowering activity. Apart from cleavage of Ang I by ACE, alternative pathways exist for the formation of Ang II, and despite ACE inhibition, a considerable amount of Ang II may be present, particularly in the heart. Because almost all known actions of Ang II are mediated via the AT₁ receptor subtype, the recently introduced specific Ang II AT₁ receptor antagonists could also be useful drugs in terms of LVH regression.
suggest a considerable effect of this class of drugs on myocardial hypertrophy and fibrosis.\textsuperscript{15,16}

The antihypertensive efficacy of the selective Ang II antagonist valsartan\textsuperscript{17} in essential hypertensive patients was shown earlier.\textsuperscript{18} We investigated the influence of 8 months of antihypertensive treatment with this Ang II antagonist on LVH versus the \( \beta \)-adrenergic receptor antagonist atenolol. \( \beta \)-Adrenergic receptor antagonists are included as first-line treatment in the recommendations of most national and international committees for the treatment of high blood pressure. Atenolol has recently been shown to be at least equally tolerable and to ensure blood pressure control comparable to that with enalapril, hydrochlorothiazide (HCTZ), and nitrendipine.\textsuperscript{19} We enrolled predominantly untreated patients to avoid the effects of previous drug treatment.

**Methods**

**Patients and Study Design**

The trial followed a randomized, double-blind, actively controlled, parallel-group design.\textsuperscript{20} The study protocol was approved by the ethics committee of the University Hospital in Frankfurt, and all study participants gave written informed consent before participation in the trial. Patients were recruited and treated by 14 general practitioners, whereas echocardiographic readings and analyses were performed at 1 central laboratory (P.K.).

One hundred seventeen previously untreated, white, hypertensive patients or those who had been treated (1) for <4 weeks during the previous 12 months or (2) with diuretics only were screened. Secondary forms of hypertension were excluded. Pretreatment with diuretics was considered acceptable, because their effect on left ventricular mass and especially wall thickness parameters has been shown to be negligible.\textsuperscript{21,22} Normal renal and liver function tests as well as blood counts were confirmed in 1 central laboratory.

The inclusion criterion was a diastolic blood pressure between 95 and 115 mm Hg and systolic blood pressure between 150 and 180 mm Hg determined after a single-blind, 3-week placebo run-in period. All blood pressure measurements were performed in duplicate with a standard cuff sphygmomanometer after 10 minutes in the sitting position. During the run-in period, the presence of LVH was established by echocardiography and defined as left ventricular mass index (LVMI) > 134 g/m\textsuperscript{2} body surface area for men and > 110 g/m\textsuperscript{2} for women and/or septal thickness > 12 mm at end diastole.\textsuperscript{23} Randomized patients received, in a double-blind manner, either valsartan 80 mg/d or atenolol 50 mg/d for the following 4 weeks. If blood pressure was not adequately controlled, ie, sitting diastolic blood pressure measured in the morning before drug intake > 95 mm Hg, the dose of both drugs was doubled. After an additional 4 weeks, HCTZ could be added in those patients in whom diastolic blood pressure still exceeded 95 mm Hg. After 3 months, the second echocardiogram was performed; regular visits were then at 8-week intervals. The final visit and third echocardiogram were performed after 8 months of double-blind treatment.

**Echocardiography**

All echocardiographic recordings were performed by 1 experienced investigator using a Hewlett Packard Sonos 1000 system with a 2.5-MHz transducer according to recommendations of the American Society of Echocardiography.\textsuperscript{24} M-mode recordings were guided by 2-dimensional views. LVMI was calculated according to the formula of Devereux et al.\textsuperscript{22} Left ventricular end-diastolic and end-systolic volumes were determined by 2-dimensional echocardiography, and left ventricular ejection and fractional shortening were calculated with standard formulas. Pulsed-wave Doppler recordings of transmitral flow velocity were performed to calculate the areas under the velocity/time curves \( fE \) and \( fA \).

Values from at least 3 beats were measured and averaged, and intraobserver variability was determined to be 6.8%, 6.2%, 3.8%, and 13% for end-diastolic septal thickness, end-diastolic posterior wall thickness, left ventricular internal diameter, and \( V_{\max }E/V_{\max }A \), respectively.\textsuperscript{24}

**Statistical Analysis**

For primary efficacy analysis, baseline and final LVMI\textsuperscript{s} were compared within treatment groups. To detect a clinically relevant change of \( \geq 15\% \) with 80% power, 26 patients were required in each treatment group, assuming a coefficient of variation of 29% and using Student’s \( t \) test on logarithmically transformed data. The level of significance was set to 5%. To compare the change in LVMI between groups, the 90% CI of the 2 ratios could be calculated with a precision of \( \pm 13\% \).

For the intention-to-treat analysis, all randomized patients having at least 1 postbaseline echocardiogram were included. The primary efficacy variable LVMI and secondary variables were analyzed after logarithmic transformation of the data by the paired \( t \) test (SAS), and the corresponding 95% CIs were calculated.

Between-treatment differences were analyzed by ANCOVA, and 95% CIs were derived. Data are given as mean \( \pm SD \); if appropriate, the median value is quoted.

A correlation analysis (Kendall) was performed between percent reduction in systolic and diastolic blood pressures, respectively, and change in LVMI. Kendall correlation coefficients (\( \tau \)) and corresponding \( P \) values are given.

**Results**

**Patients**

One hundred seven patients underwent a baseline echocardiogram; 69 met the inclusion criteria (Table 1). The known duration of hypertension was maximally 8 years (median, 17 months). Two patients were pretreated with diuretics, and 11

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Data of 69 Randomized Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Valsartan (n=34)</td>
</tr>
<tr>
<td>Atenolol (n=35)</td>
</tr>
<tr>
<td>Values are mean±SD.</td>
</tr>
</tbody>
</table>

Society of Echocardiography.\textsuperscript{25} M-mode recordings were guided by 2-dimensional views. LVMI was calculated according to the formula of Devereux et al.\textsuperscript{22} Left ventricular end-diastolic and end-systolic volumes were determined by 2-dimensional echocardiography, and left ventricular ejection and fractional shortening were calculated with standard formulas. Pulsed-wave Doppler recordings of transmitral flow velocity were performed to calculate the areas under the velocity/time curves \( fE \) and \( fA \).

Values from at least 3 beats were measured and averaged, and intraobserver variability was determined to be 6.8%, 6.2%, 3.8%, and 13% for end-diastolic septal thickness, end-diastolic posterior wall thickness, left ventricular internal diameter, and \( V_{\max }E/V_{\max }A \), respectively.\textsuperscript{24}

**Statistical Analysis**

For primary efficacy analysis, baseline and final LVMI\textsuperscript{s} were compared within treatment groups. To detect a clinically relevant change of \( \geq 15\% \) with 80% power, 26 patients were required in each treatment group, assuming a coefficient of variation of 29% and using Student’s \( t \) test on logarithmically transformed data. The level of significance was set to 5%. To compare the change in LVMI between groups, the 90% CI of the 2 ratios could be calculated with a precision of \( \pm 13\% \).

For the intention-to-treat analysis, all randomized patients having at least 1 postbaseline echocardiogram were included. The primary efficacy variable LVMI and secondary variables were analyzed after logarithmic transformation of the data by the paired \( t \) test (SAS), and the corresponding 95% CIs were calculated.

Between-treatment differences were analyzed by ANCOVA, and 95% CIs were derived. Data are given as mean \( \pm SD \); if appropriate, the median value is quoted.

A correlation analysis (Kendall) was performed between percent reduction in systolic and diastolic blood pressures, respectively, and change in LVMI. Kendall correlation coefficients (\( \tau \)) and corresponding \( P \) values are given.

**Results**

**Patients**

One hundred seven patients underwent a baseline echocardiogram; 69 met the inclusion criteria (Table 1). The known duration of hypertension was maximally 8 years (median, 17 months). Two patients were pretreated with diuretics, and 11

<table>
<thead>
<tr>
<th>TABLE 2. Number of Patients With Concomitant Chronic Diseases and Number of Patients Receiving Chronic Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan, n</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Arthritis, osteoarthritis</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Diabetes type II</td>
</tr>
<tr>
<td>Thyroid disease</td>
</tr>
<tr>
<td>Hyperuricemia</td>
</tr>
<tr>
<td>Total n=69 randomized patients.</td>
</tr>
</tbody>
</table>
patients had received other blood pressure–lowering drugs for
<4 weeks in the 12 months before the study. Concomitant
diagnoses and medications are given in Table 2. In addition,
9 patients received acetylsalicylic acid and paracetamol for
relief of common cold symptoms.

Three patients in each treatment group discontinued the
study because of adverse events: under valsartan, 1 female
patient developed a probably drug-induced bilateral dermati-
tis of the breast, 1 patient had a subarachnoid hemorrhage,
and in 1 patient a brain tumor was diagnosed. Under atenolol,
2 patients experienced angina and 1 patient dyspnea, the latter
possibly associated with atenolol. Safety blood chemistry
parameters revealed no variations in the mean and median
values, especially for serum creatinine and urea, as well as
blood lipid profiles, with the exception of 1 patient receiving
atenolol 100 mg/d plus HCTZ, in whom a clinically relevant
increase of serum uric acid, creatinine, and urea occurred.

Fifty-eight patients (n=29 in each treatment group) were
evaluable for the intention-to-treat analysis of LVH; echocar-
diographic data and blood pressure values for these patients
are presented.

Blood Pressure Control
In the valsartan treatment group, a dose increment to 160
mg/d was required in 14 patients, and 9 patients required
additional medication with HCTZ. In the atenolol group, 16
patients received 100 mg/d, and in 8 patients, addition of
HCTZ was necessary to achieve a satisfactory blood pressure
control.

After 8 months of valsartan treatment, systolic blood
pressure decreased from 163±12 to 146±13 mm Hg (mean,
–17 mm Hg; 95% CI, –21 to 13 mm Hg; P<0.0001), diastolic
blood pressure decreased from 101±6 to 90±7 mm Hg (mean,
–11 mm Hg; 95% CI, –14 to 8 mm Hg; P<0.0001). Treatment
with atenolol resulted in a decrease of systolic blood pressure from 160±14 to 147±18 mm Hg (mean,
–13 mm Hg; 95% CI, –18 to 7 mm Hg; P<0.0001), and
diastolic blood pressure was reduced from 103±6 to 90±7 mm Hg (mean,
–12 mm Hg; 95% CI, –15 to 9 mm Hg; P<0.0001).

Heart rate remained almost unchanged under valsartan
treatment at 76 bpm (median value) before treatment and 73
bpm after 8 months of treatment, whereas under atenolol, an
expected marked decrease from 76 to 64 bpm was observed.

Echocardiographic Data
After 3 months of valsartan therapy, LVMI decreased
slightly, from 127±23 to 119±23 g/m², whereas a significant
decrease could be observed after 8 months to 106±25 g/m²

TABLE 3. M-Mode and 2-Dimensional Echocardiographic Parameters
(mean±SD) Obtained During the Study (Intention-to-Treat Analysis, n=29 in
Each Treatment Group)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>8 mo, R (95% CI)</th>
<th>Baseline</th>
<th>8 mo, R (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI, g/m²</td>
<td>127±23</td>
<td>106±25‡</td>
<td>127±25</td>
<td>117±27*</td>
</tr>
<tr>
<td></td>
<td>0.83 (0.79–0.87)</td>
<td>0.92 (0.86–0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWTd, mm</td>
<td>13.6±0.7</td>
<td>12.4±1.0‡</td>
<td>13.6±1.3</td>
<td>12.8±1.0†</td>
</tr>
<tr>
<td></td>
<td>0.91 (0.88–0.93)</td>
<td>0.95 (0.92–0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVSd, mm</td>
<td>13.7±1.2</td>
<td>12.2±1.1‡</td>
<td>13.4±1.0</td>
<td>12.4±0.7‡</td>
</tr>
<tr>
<td></td>
<td>0.89 (0.87–0.92)</td>
<td>0.93 (0.91–0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVIDd, mm</td>
<td>47.24±5.13</td>
<td>46.22±5.54</td>
<td>47.56±5.08</td>
<td>47.71±4.72</td>
</tr>
<tr>
<td>LVIDs, mm</td>
<td>29.07±4.83</td>
<td>28.46±4.15</td>
<td>29.91±5.18</td>
<td>29.51±3.66</td>
</tr>
<tr>
<td>FS, %</td>
<td>39±8</td>
<td>38±6</td>
<td>37±6</td>
<td>38±5</td>
</tr>
<tr>
<td></td>
<td>1.01 (0.92–1.10)</td>
<td>1.02 (0.94–1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>91.00±27.38</td>
<td>94.97±21.94</td>
<td>98.31±21.28</td>
<td>96.34±23.09</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>32.31±15.67</td>
<td>34.07±11.59</td>
<td>35.69±13.15</td>
<td>34.00±13.42</td>
</tr>
<tr>
<td>EF, %</td>
<td>65±10</td>
<td>65±7</td>
<td>64±9</td>
<td>65±9</td>
</tr>
<tr>
<td></td>
<td>1.00 (0.94–1.07)</td>
<td>1.02 (0.95–1.10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PWTd indicates end-diastolic posterior wall thickness; IVSd, end-diastolic septal wall thickness;
LVIDd, left ventricular end-diastolic diameter; LVIDs, left ventricular end-systolic diameter; FS,
fractional shortening; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic
volume; and EF, ejection fraction.

*P<0.01 vs baseline; †P=0.005 vs baseline; ‡P<0.0001 vs baseline.
Table 4. Doppler Echocardiographic Parameters (mean±SD) Obtained During the Study (Intent-to-Treat Analysis, n=29 in Each Treatment Group)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Valsartan</th>
<th>Atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>VeeA, cm/s</td>
<td>75.30±18.27</td>
<td>70.14±12.42</td>
</tr>
<tr>
<td>VeeA, cm/s</td>
<td>82.64±19.35</td>
<td>78.07±16.48</td>
</tr>
<tr>
<td>fE, cm</td>
<td>10.76±3.02</td>
<td>11.61±2.33</td>
</tr>
<tr>
<td>fA, cm</td>
<td>10.66±2.98</td>
<td>10.46±2.60</td>
</tr>
<tr>
<td>fE/fA</td>
<td>1.06±0.33</td>
<td>1.16±0.29</td>
</tr>
</tbody>
</table>

Vee indicates maximal velocity of early diastolic filling phase; VeeA, maximal velocity of late diastolic filling phase; fE, time/velocity integral of early diastolic filling phase; fA, time/velocity integral of late diastolic filling phase; and fE/fA, ratio of the integrals.

*P<0.01 vs baseline.

Table 5. Correlation Coefficients Between Percent Reduction of Blood Pressure and Decrease in LVMI (Kendall Correlation Coefficient, \( \tau \))

<table>
<thead>
<tr>
<th></th>
<th>Valsartan, ( \tau ) (P)</th>
<th>Atenolol, ( \tau ) (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% reduction in diastolic BP vs % decrease in LVMI</td>
<td>0.195 (0.14)</td>
<td>-0.193 (0.14)</td>
</tr>
<tr>
<td>% decrease in systolic BP vs % decrease in LVMI</td>
<td>0.197 (0.13)</td>
<td>-0.032 (0.81)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

Discussion

The prevalence of LVH has recently been estimated to be 62% in essential hypertensive patients with a sitting diastolic blood pressure between 100 and 115 mm Hg, which is in accordance with our screening results. In contrast to 3 previous studies in patients with LVH who were given the Ang II antagonist losartan, we observed a significant reduction in left ventricular mass after 8 months of treatment with the Ang II antagonist valsartan. As in our study, Cheung included only previously untreated patients, but as in the investigation by Himmelmann et al., treatment duration was only 12 weeks. However, the most marked effect on LVMI, and especially the difference versus atenolol, occurred between 3 and 8 months of treatment with valsartan. Baseline values of LVMI were comparable between our study and these 2 studies; however, in the long-term (29-month) study reported by Himmelmann and coworkers, patients were pretreated and had a normal baseline LVMI of 97 g/m². One should consider that in the other investigations, the number of patients enrolled ranged between 12 and 24 patients.

The overall extent of reduction in LVMI observed in our trial is comparable to that of other studies. In a comparative trial between the ACE inhibitor ramipril and atenolol, 6 months of treatment with atenolol induced only a minor regression of LVMI, from 139 to 133 g/m²; in contrast, ramipril produced a significant reduction, from 136 to 117 g/m². The reduction of 19 g/m² obtained with the ACE inhibitor appears to be comparable to our results with an AT₁ antagonist.

We found no significant correlation between blood pressure reduction and decrease in left ventricular mass, possibly because of the sample size and the large variability of findings. However, there was a trend for a positive correlation for valsartan, but not for atenolol. In 206 essential hypertensive patients receiving lisinopril and additional HCTZ, no correlation could be demonstrated between change in clinic sitting blood pressure and change in LVMI, whereas a close correlation was found between decrease in average 24-hour ambulatory blood pressure values and reduction in LVMI.

In renovascular hypertensive rats, Zierhut et al observed a significant decrease of LVMI after 12 weeks of treatment with valsartan, comparable to the effect induced by an ACE inhibitor. Treatment with the Ang II antagonist TCV-116 prevented the development of LVH in the spontaneously hypertensive rat model by reducing left ventricular wall thickness and weight and also interstitial fibrosis.

It has been suggested that AT₁ antagonists, like ACE inhibitors, possess a pharmacological effect beyond blood pressure reduction, in which blockade of the AT₁ receptor may lead to an attenuation of the growth-promoting actions of Ang II.
However, little is known about the presence and role of the AT₂ receptor subtype (and other subtypes) in patients with LVH. Liu and coworkers showed, in rats after myocardial infarction, that a considerable share of the beneficial effects of an Ang II AT₁ receptor antagonist could be attenuated by additional treatment with an AT₂ antagonist. These findings indicate that stimulation of the AT₂ receptor plays an important role in the mechanism of action of selective AT₁ receptor antagonists. Irrespective of the mechanism of action, the ELITE trial demonstrated that the Ang II antagonist losartan is at least as effective as an ACE inhibitor with regard to prevention of heart failure–related hospital admissions and reduction of total mortality.

Some aspects of our study may be considered to be shortcomings. First, treatment duration was restricted to 8 months. Liebson and coworkers described an additional decrease of left ventricular mass after 12 months of treatment with different antihypertensive drug classes.

The method of measuring LVMi by echocardiography requires some comment. The reproducibility of 2-dimensional and M-mode echocardiography has been validated in our echocardiography laboratory, and variability is in accordance with recently published data on the quality of echocardiographic readings.

Confirming experimental data, a considerable regression of LVMI was obtained after 8 months of treatment with the Ang II antagonist valsartan in essential hypertensive patients, indicating that valsartan may safely be given to patients with LVH. The long-term clinical benefit of the LVH reduction obtained after chronic treatment with Ang II antagonists has to be elucidated in clinical studies using end points such as cardiovascular events and mortality.

Appendix

Participating General Practitioners

K. Albrecht, S. Mörsch (Undenheim); E. Bakker (Gründau); F. Criveanu (Frankfurt); A. Faust (Mainz); F. Frohnapfel (Ludwigshafen); G. Härtter, V. Rudie (Reißen); V. Janevskovic (Frankfurt); E. Reichwein (Villmar); R. Santo (Lahnau); A. Schmidt (Offenbach); R. Schneider (Wetzlar); M. Stoll, A. Dietz (Dreieich); R. Will (Frankfurt); W. Oldenburg (Frankfurt), Germany.

Acknowledgments

We thank Florence Botteri, PhD, Novartis Pharma AG, Switzerland, for her advice and Doris Bach, PhD, Novartis Pharma AG, Switzerland, for statistical evaluations.

References


Influence of the Angiotensin II Antagonist Valsartan on Left Ventricular Hypertrophy in Patients With Essential Hypertension
Petra A. Thürmann, Peter Kenedi, Andor Schmidt, Sebastian Harder and Norbert Rietbrock

Circulation. 1998;98:2037-2042
doi: 10.1161/01.CIR.98.19.2037

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/98/19/2037

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/